REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 11-13, 16, 18-21, 23 and 24, the only claims pending and currently under examination in this application.

Double Patenting

Claims 11-13, 16, 18-21, 23 and 24 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims 1, 15, 17, 26 and 27 and specification of copending U.S. Patent Application No. 09/858,332 (Publ. No. 20020164718 A1). While Applicant does not acquiesce to the validity of the rejection, Applicant hereby submits the accompanying Terminal Disclaimer with respect to U.S. Patent Application Serial No. 09/858,332 (Publ. No. 20020164718 A1) in order to move the prosecution of the pending claims forward. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claim Rejections – 35 USC § 103

The Examiner rejects Claims 11-13, 16, 18-21, 23 and 24 under 35 U.S.C. § 103(a) as being unpatentable over Tchaga et al. (WO 99/57992) in view of Porath et al. (Biochemistry, 1983: 22; p.1621-1630). In making this rejection, the Examiner has asserted that Tchaga et al. teaches all of the elements of the claimed invention but for the use of multiple columns, for which element the Examiner looks to Porath et al. The Applicants respectfully traverse the rejection.

Tchaga et al. teaches that the use of fusion proteins containing metal ion affinity peptides in the context of a single-ion column can result in purification of up to 95-98% in a single chromatography step, with recovery generally being higher than 85% (Tchaga et al., page 2, paragraph 4). Tchaga et al. demonstrates a greater than 95% recovery of lactate dehydrogenase activity using such a protocol (Examples 2 and 4;

page 12, line 26 and page 15, line 16). The addition of the ion affinity peptide which efficiently complexes metal ions is taught as the mechanism of increased specificity and adsorption affinity, as it **prevents the participation of the native protein in adsorption** (page 2, paragraph 3). The ordinarily skilled artisan thus finds no motivation in Tchaga et al. to improve upon such a protocol, nor any suggestion therein that the use of a second column or a different metal ion would be a means to do so.

The Applicants note that Porath et al.(1983) describes the use of columns packed with agarose chelator gels loaded with different metal ions linked in tandem in order to separate **untagged** serum proteins. Here, the **adsorption is mediated entirely by the native protein**, by a mechanism which is poorly understood. The affinities of specific metal ions for specific features of the bound protein are broadly theorized but are not known. In Porath et al., the rationale for using multiple metal ions stems from the need to **vary the specificity of adsorption** of different protein components of the sample so that they may be eluted in stepwise fashion by incremental variations in pH. The primary goal is maximizing specificity and thus attrition of undesired protein fractions, not high-efficiency recovery.

Furthermore, Porath et al. teaches tandem columns in the context of untagged proteins native proteins, where adsorption to the column is based on different proteins affinities for the column. In the context of tagged proteins which are bound by virtue of the same common tag, one would not expect any benefit to be obtained by using tandem columns as opposed to one column, because all the proteins are tagged with the same tag.

There is thus no obvious suggestion or motivation for one of ordinary skill in the art to combine the method of Porath et al. with an already highly efficient method such as that taught by Tchaga et al., wherein specificity is overwhelmingly mediated by the fused metal ion affinity peptide. The Applicants submit that the suggestion to combine the cited references is absent from the references themselves, neither reference

describing nor suggesting the assembly of kits for purifying a protein with both a first and second metal ion chelate resin **in combination with** a recombinant vector which facilitates the fusion of a heterologous molecule to a metal ion affinity peptide as presently claimed. Such a suggestion could only come in light of the apprehension and description of the problem of providing a suitable means for purifying proteins fused to affinity peptides to a higher degree of specificity, a discussion of which problem is found in the present specification and is absent from the cited art, the inventive solution to which is disclosed in the present application.

The Applicants further note that Porath et al. was published 18 years before the priority date of the present application, yet the contents of the presently claimed invention remain novel, notwithstanding the statement in the Office Action that this design strategy is known and commonly used in the art.

The Applicants therefore submit that the analysis provided in the Office Action is a hindsight reconstruction of the invention claimed in this application from particular elements of the cited references taken out of context. The courts have said that this type of analysis is prohibited. Hindsight is not a justifiable basis on which to find that the ultimate achievement of a long sought and difficult scientific goal was obvious. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), cert. denied, 502 U.S. 856 (1991).

Specifically, a prior art reference must be read in its entirety for all that it teaches. The courts prohibit hindsight reconstruction of a different invention by cherry-picking particular elements of the prior art reference, and making them work together in a manner that is different from what an individual reference intends. It is insufficient that the prior art disclosed the components of the presently claimed kit, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the **combination** made by the inventor. *Northern Telecom, Inc. v. Datapoint Corp. 15 USPQ2d 1321* (Fed. Cir. 1990), cert. denied, 498 U.S. 920 (1990).

Absent from the cited art, both individually and in combination, is the insight that the use of multiple metal ions could improve the efficient chromatographic separation of already affinity-tagged proteins. The claims presented herein specifically recite this inventive feature and are therefore patentable over the combination of Tchaga et al. and Porath et al.

Accordingly, Claims 1-10 and 21-25 are not obvious under 35 U.S.C. § 103(a) over Tchaga et al. in view of Porath et al. and this rejection may be withdrawn.

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CONCLUSION

In view of the amendments and remarks above, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CLON-056US2.

Respectfully submitted,

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Date: May 30, 2006

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Terminal Disclaimer over U.S. Patent Application Serial No. 09/858,332

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